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CASE REPORT

PRIMARY ASPERGILLOMA AND SUBACUTE INVASIVE ASPERGILLOSIS IN TWO AIDS PATIENTS

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SUMMARY

Although uncommon, invasive aspergillosis in the setting of AIDS is important because of its peculiar clinical presentation and high lethality. This report examines two AIDS patients with a history of severe cellular immunosuppression and previous neutropenia, who developed subacute invasive aspergillosis. One female patient developed primary lung aspergilloma, with dissemination to the mediastinum, vertebrae, and spine, which was fatal despite antifungal treatment. The second patient, who had multiple cavitary brain lesions, and eye and lung involvement, recovered following voriconazole and itraconazole, and drugs for increasing neutrophil and CD4+ lymphocyte levels. These cases demonstrate the importance of *Aspergillus* infections following neutropenia in AIDS patients, and emphasize the need for early and effective antifungal therapy.

KEYWORDS: Aspergilloma; Acquired immunodeficiency syndrome; Central nervous system; Invasive aspergillosis; Neutropenia.

INTRODUCTION

Aspergillus species can be cause of different lung diseases, including allergic bronchopulmonary aspergillosis, aspergilloma, chronic invasive pulmonary infection, and acute invasive infection. Immunocompromised patients are more susceptible to invasive *Aspergillus* disease. This is particularly true for patients with neutropenia, reduced neutrophil activity, reduced hematopoietic stem cells, and those with a history of solid organ transplantation, corticosteroid therapy, or cytotoxic chemotherapy. Although infrequent in HIV-infected patients (0 to 12% prevalence at autopsy), the disease is highly lethal in advanced AIDS[3,5]. In HIV-infected patients, *Aspergillus* pulmonary lesions are characterized by interstitial or alveolar infiltrates, nodules, cavities, abscesses, hemorrhagic infarction, or pleural discharge[6,18]. The central nervous system may also be secondarily involved in AIDS patients[7,16,24]. Invasive aspergillosis less frequently involves the sinuses, orbit, eye, heart or other viscera[8,13,17,19,25]. Primary cutaneous lesions[2,14] and isolated tracheobronchitis[23] have been reported. A previous study reported aspergillosis diagnosed between 10 and 26 months following onset of AIDS; despite anti-fungal therapy, these patients died within two to four months[6].

This case series describes two patients who developed subacute invasive *Aspergillus* infection in the setting of AIDS, one in the form of invasive pulmonary mycetoma and the other as a primary opportunistic disease.

CASE REPORTS

Case 1: The patient was a 33-year-old housewife diagnosed with HIV in 1997. She refused antiretroviral treatment at this time. In September 1999, the patient developed pneumonia and was subsequently treated with zidovudine, lamivudine and indinavir, as well as trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* prophylaxis (105 CD4 cells/μL). Trimethoprim/sulfamethoxazole was discontinued and stavudine substituted for zidovudine in January 2000 because the patient developed anemia and leukopenia (572 neutrophils/μL) in the last two months. In June 2000, the antiretroviral regimen was changed to didanosine, lamivudine and nelfinavir after the patient developed sinusitis, oral candidiasis, and esophageal candidiasis.

In September 2000, the patient developed a productive cough, and a chest x-ray showed a right upper lung lobe cavitation. Although microscopy did not demonstrate acid fast bacilli, the patient was presumptively treated for tuberculosis with rifampicin, isoniazid and pyrazinamide. Antiretrovirals were withheld during this time.

Two months later, her symptoms persisted and she had lost two kilograms. Her neutrophil count had increased to 1512 cells/μL, and chest x-ray and computed tomography (CT) showed a cavity with a fungus ball inside, compatible with a pulmonary mycetoma. Repeated microscopic examination and sputum culture were negative for mycobacteria

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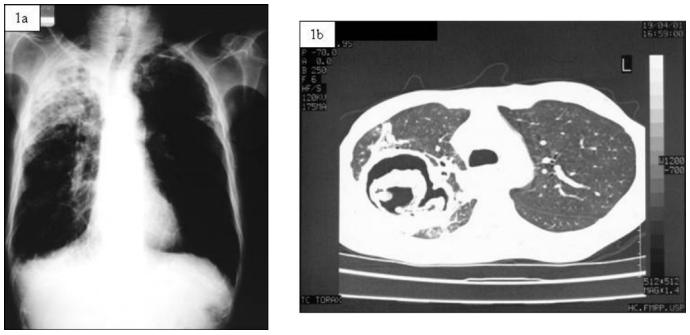

Fig. 1 - Case 1: (a) Pre-lobectomy chest x-ray shows a large cavity-contained aspergilloma in the right upper lung lobe; (b) CT thorax showing signs of air crescent and invasion of pulmonary parenchyma and pleura.

but positive for *Aspergillus fumigatus.* The patient's antibodies anti-*Aspergillus* titer was 1:64. Itraconazole 400 mg PO, daily, was added, and an antiretroviral regimen of zidovudine, lamivudine, saquinavir and ritonavir was started.

In April 2001, the patient weighed 40 kg, and complained of a persistent cough, foul-smelling sputum, fever, and pain in the right upper chest. HIV1 viral load was 220,000 copies/μL, and CD4+ count was 18 cells/μL. The inflammatory infiltrate had involved the entire right upper lung lobe (Fig. 1a) and a new CT showed a large aspergilloma with air crescent sign and invasion of the surrounding lung parenchyma (Fig. 1b). *A. fumigatus* was isolated from the sputum, and anti-*Aspergillus* titers remained at 1:64.

The patient received ceftriaxone and amphotericin B deoxycholate (2,200 mg) for presumed invasive aspergillosis with secondary bacterial infection and underwent surgical resection of the right upper lung lobe. Histologic analysis of lobectomy material revealed a granulomatous chronic inflammatory process, presence of *Aspergillus* hyphae, and cytological alterations suggestive of cytomegalovirus. The patient recovered following surgery and felt well until August 2001, when she developed a productive cough, chest pain and tachypnea.

In the following weeks, the patient presented with lower limb paresthesia, paraparesis, and urinary incontinence. Soon thereafter her condition deteriorated and she developed pneumonia. *A. fumigatus* was identified in many sputum cultures. A CT of the thorax showed bilateral reticulonodular infiltrates with mediastinal lymphadenopathy (Fig. 2a). Magnetic resonance imaging (MRI) of the spine revealed T4 to T6 vertebral and intervertebral disk destruction, with spinal cord involvement (Fig. 2b). Despite receiving another course of amphotericin B (340 mg), the patient died in October 2001.

Case 2: The patient was a 32-year-old male pharmacist who had been without medical care since his HIV diagnosis one year prior. For four months prior to presentation, he experienced behavioral changes, including forgetfulness and irritability. A head CT showed hypodense non-enhancing lesions, and presumptive treatment for cerebral toxoplasmosis was started. After 25 days of treatment, the patient showed no evidence of clinical or radiologic improvement. A stereotactic brain biopsy showed white matter demyelination, suggestive of progressive multifocal leukoencephalopathy. Treatment with corticosteroids,

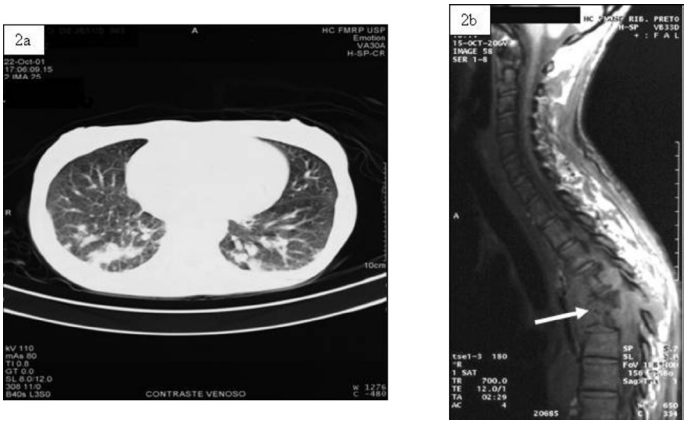

Fig. 2 - Case 1: (a) Post-lobectomy thoracic CT showing bilateral pulmonary invasion by *Aspergillus;* (b) MRI spine showing vertebral and intervertebral disk destruction at the T4 to T6 level.

zidovudine, lamivudine, lopinavir/ritonavir, dexamethasone and carbamazepine was initiated.

In December 2006, eight months after onset of symptoms, the patient was admitted in São Paulo University Hospital at Ribeirão Preto, SP. Behavioral alterations persisted and he had a 20-day history of left-eye hyperemia and purulent discharge. On exam, the patient was confused, with left palpebral ptosis and oral candidiasis. At admission, laboratory data were as follows: hemoglobin 6.6 g/dL; leukocytes 1500 cells/μL; 800 neutrophils/ μL; 194,000 platelets/μL; and alanine aminotransferase 49 UI/L. The level of the HIV1 viral load was less than 50 copies/mL and the CD4+ count was 84 cells/μL. Intraocular puncture yielded vitreous material containing *Aspergillus.* A CT of the thorax showed a thick-walled cavity with peripheral aspergilloma in the right upper lobe (Fig. 3a). An MRI of the brain showed cavitary lesions in the left frontal, left parietal, left temporal, and right parieto-occipital lobes, as well as endophthalmitis in the left eye (Fig. 3b). Cerebrospinal fluid (CSF) evaluation showed: 2.6 cells/mL; protein 61.9 mg/dL; glucose 60 mg/dL. CSF cultures were negative for bacteria and fungi.

Treatment with amphotericin B deoxycholate (total dose: 230 mg), was interrupted due to severe pancytopenia (hemoglobin 5.2 g/dL; leukocytes 400 cells/μL; neutrophils 0 cells/μL; platelets 86,000/μL).

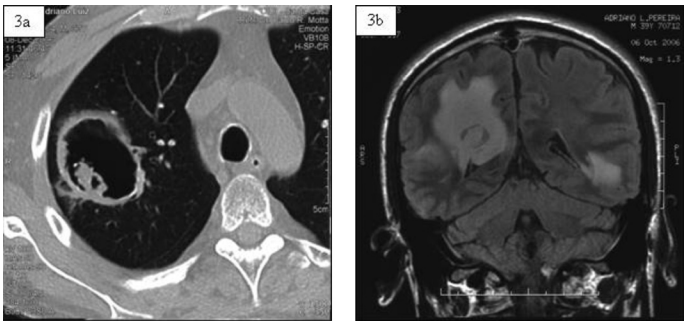

Fig. 3 - Case 2: (a) Pre-treatment thoracic CT showing thickened wall cavity and peripheral aspergilloma; (b) Pre-treatment MRI brain showing bilateral cerebral hemisphere lesions and central cavitation.

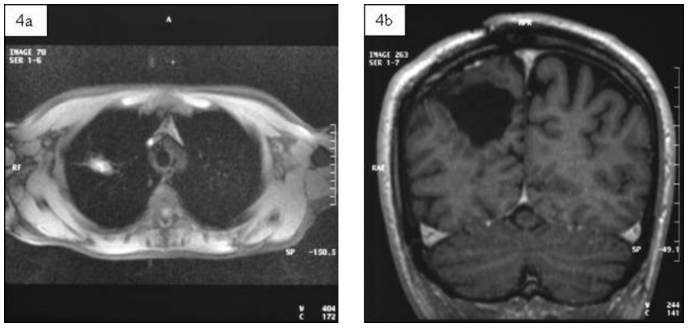

Fig. 4 - Case 2: a) Thoracic MRI showing residual nodule following treatment; (b) Post-treatment MRI brain demonstrates a parietal cavity signal intensity similar to CSF. Areas of gliosis and accentuated groves are noted in the adjacent cerebral parenchyma.

A bone marrow biopsy showed aplasia. At that time, zidovudine was replaced with abacavir, and the patient received granulocyte colony stimulating factor (G-CSF) and red blood cell transfusions. Voriconazole P.O. 400 mg daily was added to replace amphotericin B. His left eye was enucleated. The patient improved clinically and laboratory values demonstrated medullar recovery (hemoglobin 11.3 g/dL; leucocytes 7000 cells/μL; neutrophils 2800 cells/μL; platelets 356,000 cells/μL) and immunologic recovery (CD4+ count 721 cells/μL). HIV1 viral load was less than 50 copies/mL. After 30 days of voriconazole, the patient was switched to itraconazole (600 mg orally daily) for eight months. Thoracic MRI showed a residual nodular area in the right upper lung (Fig. 4a). Brain MRI showed a liquid-filled cavity in the parietal region of the brain (Fig. 4b).

DISCUSSION

These cases of subacute invasive infection are characteristic of *Aspergillus* in the setting of AIDS. In case 1, a primary lung aspergilloma was initially misdiagnosed as tuberculosis. Mycetoma formation with invasion of adjacent pulmonary tissue occurred during treatment with anti-tuberculosis drugs. Temporary improvement following antifungal therapy and surgery was followed by *Aspergillus* recurrence, dissemination to the vertebral column and spinal medulla, and eventual death.

The second patient, who presented with neurological symptoms, was initially misdiagnosed with neurotoxoplasmosis. Brain lesions worsened and lung lesions and endophthalmitis appeared despite sulfadiazine and pyrimethamine treatment. Although the patient lost the infected eye, he survived due to antifungal treatment and granulocyte and lymphocyte recovery.

AIDS patients infected with *Aspergillus* experience prolonged immunosuppression and higher numbers of opportunistic infections than AIDS patients without aspergillosis[26]. Predisposing factors in invasive aspergillosis include neutropenia, pneumocystosis and other pulmonary diseases, broad spectrum antibiotic therapy, use of corticoids or marijuana, and alcoholism[15,21]. In these two cases, *Aspergillus* infections were facilitated by low CD4+ cell counts and prolonged neutropenia resulting from antiretroviral and antiparasitic drug use.

It is interesting to note that aspergillosis can manifest clinically following resolution of neutropenia (regardless of HIV status)[14,22]. The presence of cytomegalovirus, incidentally found in the lung of the first patient, has also been implicated in the development of pulmonary aspergillosis[18,26].

Most AIDS patients develop acute invasive pulmonary aspergillosis, with rapid evolution and hematogenous spread. In some AIDS patients aspergillosis may have a subacute or chronic course[18], as observed in the cases reported here. It is possible that absolute neutrophil counts greater than 500 cells/μL and preserved capacity of recuperation of the bone marrow protect patients from an acute development of aspergillosis. In immunocompetent persons, *Aspergillus* often presents as an aspergilloma. However, this is infrequent in AIDS patients. When they do occur, 50% of lesions progress rapidly to invasive pulmonary disease, which is associated with a poor prognosis[4,12,23]. Respiratory symptoms and fever are more common in *Aspergillus* infection in AIDS than in patients without HIV infection[1].

Positive cultures for *Aspergillus* spp. in respiratory secretions may be considered in AIDS patients with pulmonary infiltrates but aspergillosis diagnosis may requires additional invasive techniques[12]. Identification of *Aspergillus fumigatus* in the first patient's sputum samples and isolation of *Aspergillus* sp. in the second patient's eye alerted the clinician to the diagnosis of aspergillosis. *A. fumigatus* is the most common species causing human disease[6]. The presence of serum antibodies to *Aspergillus* may aid in diagnosis of some HIV-infected patients, but immunocompromised persons may not have detectable antibody levels[3].

The death of the first patient highlights the poor response to treatment and high lethality characteristic of aspergillosis in the setting of AIDS[15]. In that patient, it is possible that itraconazole plasma levels were depressed by concurrent administration of rifampicin. Regardless, the persistence of *A. fumigatus* following prolonged amphotericin B therapy illustrates the difficulty in obtaining mycologic cures in immunosuppressed patients. The second patient was cured by the treatment with voriconazole followed by consolidation therapy with itraconazole. It is believed that highly active voriconazole, in combination with immunologic and hematologic recovery were responsible for this patient's survival[21]. Voriconazole and other new antifungals may improve outcomes for HIV and *Aspergillus* co-infected patients in the future[10,11].

Opportunistc aspergillosis complicating AIDS patients presents a diagnostic and therapeutic dilemma because of its peculiar clinical characteristics and unfavorable evolution. Clinical suspicion of *Aspergillus* infection should be accompanied by rapid diagnostic evaluation using microscopy, culture, and invasive procedures if necessary. Early recognition and detection are essential for timely initiation of potentially life-saving antifungal therapy and of drugs for phagocytosis and cellular immunity recovery.

RESUMO

Aspergiloma primário e aspergilose invasiva subaguda em dois pacientes com AIDS

A aspergilose invasiva em pacientes com aids, embora incomum, é relevante pela apresentação clínica peculiar e alta letalidade. Este relato descreve os casos de dois pacientes com aids com grave imunossupressão

celular e neutropenia prévia, os quais tiveram aspergiloma pulmonar primário, com disseminação para mediastino, vértebras e medula espinhal, evoluindo para óbito apesar do tratamento antifúngico. O segundo paciente, que tinha lesões cavitárias múltiplas no cérebro e infecção ocular e pulmonar, recuperou-se após tratamento com voricanazol, itraconazol e com drogas para aumentar o número de neutrófilos e de linfócitos $CD4^+$. Estes casos demonstram o risco de infecção por *Aspergillus* após episódios de neutropenia em pacientes com aids e alertam para o início precoce de terapia antifúngica eficaz.

REFERENCES

1. ADDRIZZO-HARRIS, D.J.; HARKIN, T.J.; McGUINNESS, G.; NAIDICH, D.P. & ROM, W.N. - Pulmonary aspergilloma and AIDS. A comparison of HIV-infected and HIV-negative individuals. **Chest, 111**: 612-618, 1997.

2. BORBUJO, J.; JARA, M.; BARROS, C.; AMOR, E. & FORTES, D. - Primary cutaneous aspergillosis in a patient with acquired immunodeficiency syndrome. **J. Europ. Acad. Derm. Vener., 12**: 268-270, 1999.

3. DENNING, D.W. - Invasive aspergillosis. **Clin. infect. Dis., 26**: 781-805, 1998.

4. GREENBERG, A.K.; KNAPP, J.; ROM, W.N. & ADDRIZZO-HARRIS, D.J. - Clinical presentation of pulmonary mycetoma in HIV- infected patients. **Chest, 122**: 886-892, 2002.

5. HOLDING, K.J.; DWORKIN, M.S.; WAN, P-C.T. *et al* - Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. **Clin. infect. Dis., 31**: 1253-1257, 2000.

6. KHOO, S.H. & DENNING, DW. - Invasive aspergillosis in patients with AIDS. **Clin. infect. Dis., 19** (suppl. 1): S41-S48, 1994.

7. KLEINSCHMIDT-DeMASTERS, B.K. - Central nervous system aspergillosis: a 20-year retrospective series. **Hum. Path., 33**: 116-124, 2002.

8. KÜMMERLE, S. & WEDLER, H. - Renal abscesses in an AIDS patient caused by *Aspergillus fumigatus*. **Urol. Int., 61**: 52-54, 1998.

9. LIBANORE, M.; PRINI, E.; MAZZETTI, M. *et al.* - Invasive aspergillosis in Italian AIDS patients. **Infection, 30**: 341-345, 2002.

10. MASCHMEYER, G.; HAAS, A. & CORNELY, O. - Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. **Drugs, 67**: 1567-1601, 2007.

11. METCALF, S.C. & DOCKRELL, D.H. - Improved outcomes associated with advances in therapy for invasive fungal infections in immunocompromised hosts. **J. Infect., 55**: 287-299, 2007.

12. MEYOHAS, M.C.; ROUX, P.; POIROT, J.L.; MEYNARD, J.L. & FRONTTIER, J. - Aspergillose au cours du syndrome d´immunodéficience acquise. **Path. Biol., 42**: 647-651, 1994.

13. MILLER, F.H. & MA, J.J. - Total splenic infarct due to *Aspergillus* and AIDS. **Clin. Imaging, 24**: 362-364, 2000.

14. MURAKAWA, G.J.; HARVELL, J.D.; LUBITZ, P. *et al* - Cutaneous aspergillosis and acquired immunodeficiency syndrome. **Arch. Derm., 136**: 365-369, 2000.

15. MYLONAKIS, E.; BARLAM, T.F.; FLANIGAN, T. & RICH, J.D. - Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. **Chest, 114**: 251-262, 1998.

16. MYLONAKIS, E.; PALIOU, M.; SAX, P.E. *et al*. - Central nervous system aspergillosis in patients with human immunodeficiency virus infection. Report of 6 cases and review. **Medicine (Baltimore), 79**: 269-280, 2000.

17. MYLONAKIS, E.; RICH, J.; SKOLNIK, P.R.; De ORCHIS D.F. & FLANIGAN, T. - Invasive *Aspergillus sinusitis* in patients with human immunodeficiency virus infection: report of 2 cases and review. **Medicine (Baltimore), 76**: 249-255, 1997.

18. NASH, G.; IRVINE, R.; KERSCHMANN, R.L. & HERNDIER, R.B. - Pulmonary aspergillosis in acquired immune deficiency syndrome: autopsy study of an emerging pulmonary complication of human immunodeficiency virus infection. **Hum. Path., 28**: 1268-1275, 1997.

19. PAULA, J.S.; BRYK Jr., A.; LAURETTI FILHO, A. & ROMÃO, E. - Secondary glaucoma associated with bilateral *Aspergillus niger* endophthalmitis in an HIV-positive patient: case report**. Arq. bras. Oftalmol., 69**: 395-397, 2006.

20. SCHWARTZ, S.; RUHNKE, M.; RIBAUD, P. *et al*. - Improved outcome in central nervous system aspergillosis, using voriconazole treatment. **Blood, 106**: 2641-2645, 2005.

21. SEGAL, B.H. & WALSH, T.J. - Current approaches to diagnosis and treatment of invasive aspergillosis. **Amer. J. respir. crit. Care Med., 173**: 707-717, 2006.

22. SHAUKAT, A.; BAKRI, F.; YOUNG, P. *et al*. - Invasive filamentous fungal infections in allogeneic hematopoietic stem cell transplant recipients after recovery from neutropenia: clinical, radiologic and pathologic characteristics. **Mycopathologia, 159**: 181-188, 2005.

23. SOUBANI, A.O. & CHANDRASEKAR, P.H. - The clinical spectrum of pulmonary aspergillosis. **Chest, 121**: 1998-1999, 2002.

24. VIDAL, J.E.; DAUAR, R.F.; MELHEM, M.S. *et al*. - Cerebral aspergillosis due to *Aspergillus fumigatus* in AIDS patient: first culture-proven case reported in Brazil. **Rev. Inst. Med. trop. S. Paulo, 47**: 161-165, 2005.

25. XIE, L.; GEBRE, W.; SZABO, K. & LIN, J.H. - Cardiac aspergillosis in patients with acquired immunodeficiency syndrome: a case report and review of the literature. **Arch. Path. Lab. Med., 129**: 511-515, 2005.

26. WOITAS, R.P.; ROCKSTROH, J.K.; THEISEN, A. *et al*. - Changing role of invasive aspergillosis in AIDS: a case control study. **J. Infect., 37**: 116-122, 1998.

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